

## Citation

Banu Preethi GOPU, Ralph Duckworth, Liane Azevedo, Murali Krishnan Perumbakkam Subramanian, Sherley John, Vida Zohoori. Association between early exposure to fluoride and cognitive outcomes in children from gestation to 18 years of age – a systematic review. PROSPERO 2021 CRD42021230649 Available from: [https://www.crd.york.ac.uk/prospERO/display\\_record.php?ID=CRD42021230649](https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42021230649)

## Review question

1. Is there an association between

a) early exposure to fluoride in mothers during pregnancy and cognitive outcomes in their children below eighteen years of age and

b) children below eighteen years' exposure to fluoride and cognitive outcomes?

## Searches

A peer-reviewed search strategy will be performed. Only published literature in the English language with human studies will be searched without any date restrictions, using the following electronic databases:

- MEDLINE via EBSCO Host
- Embase via EBSCO Host
- PubMed
- The Cochrane Database of Systematic Reviews
- CINAHL via EBSCO Host
- Web of Science
- Scopus.
- PsycINFO

These sources will be searched for all articles containing keywords and text terms relating to fluoride exposure in mothers during pregnancy and children below the age of 18, and cognitive outcomes such as IQ, ADHD, focussed, sustained, shifting and encoding attention, academic achievements in children below 18 years, adapted for each bibliographic database syntax rules. The resulting set of references will be imported into EndNote reference management software, and duplicates will be removed. In addition, the reference list of all included studies will be searched for additional studies that are not identified by the electronic search.

## Types of study to be included

Inclusion:

We will include observational (both longitudinal, cross-sectional) and experimental studies focused on the association between fluoride exposure and cognitive outcomes in children below eighteen years.

Exclusion:

Studies on animals and children above eighteen years of age will not be included. Also, case studies, narrative reports, expert opinion, reviews, abstracts without full texts and conference presentations will not be eligible for inclusion.

### Condition or domain being studied

The role of fluoride in the prevention of dental caries is widely recognised. However, chronic, excess intake of fluoride causes dental fluorosis and skeletal fluorosis. Multiple studies suggest that fluoride crosses the placenta and it accumulates in the brain and affects the central nervous system.

The human brain increases in size four-fold during the preschool period, reaching approximately 90% of adult volume by six years. Gene expression and environmental input are essential for normal brain development, and disruption of either can fundamentally alter neural outcomes.

Increased maternal urinary fluoride concentration is also associated with more attention-deficit/ hyperactivity disorder-like symptoms in children. In a systematic review, including 38 studies of fluoride exposure and children's IQ, the weighted mean effect size between regions of higher and lower fluoride exposure was equivalent to 6.9 IQ points. Sensitivity analyses showed that the adverse effects on children's intelligence remained significant(9).

Although systematic reviews have been conducted on the relationship between fluoride exposure and cognitive outcomes in children 4-16 years of age, no review exists investigating the association between maternal fluoride exposure and cognitive outcomes in their offspring. The review will examine this in children and association between fluoride exposure in children and cognitive outcomes.

### Participants/population

This review will include research studies which are conducted among pregnant women and children below the age of eighteen, who have directly or indirectly been exposed to fluoride.

### Intervention(s), exposure(s)

Any source of fluoride

### Comparator(s)/control

Not applicable

### Context

No restrictions

### Main outcome(s)

Validated measures of cognitive outcomes (such as but not limited to focussed, sustained, shifting and encoding attention), academic achievements will form the primary outcomes. For example, the following measures could have been used in the eligible studies:

Wechsler Intelligence Test for Children (Digit span, Arithmetic, Coding, Digit Symbol; WISC)

The Test of Everyday Attention for Children (TEA-CH)

The Continuous Performance Test (CPT)

The Wisconsin Card Sorting Test (WCST)

Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-IV)

Achenbach Child Behaviour Checklist (CBCL)

### Measures of effect

As used in the eligible studies.

### Additional outcome(s)

Cognitive ability, educational achievement, verbal ability

### Measures of effect

As measured using relevant tools

### Data extraction (selection and coding)

Selection of studies:

All observational and experimental studies based on the association between fluoride exposure and cognitive outcomes in children below eighteen years will be searched in databases. The results will be screened by two reviewers who will independently screen all relevant citations retrieved from the database search at the title and abstract screening stage. This will be followed by screening full text articles, which focuses on the association between fluoride exposure and cognitive outcomes in children below eighteen years. Animal studies and studies containing children above eighteen years of age will be excluded in the review, along with case studies, narrative reports, expert opinion, reviews, abstracts without full texts and conference presentations. A third reviewer will resolve any disagreements through discussion until consensus is reached upon completing the full text screening.

Data extraction and management:

One reviewer will independently extract the data relating to Cognitive outcomes (such as but not limited to focussed, sustained, shifting and encoding attention), sociodemographic characteristics and type of fluoride exposure with a custom-designed data extraction table which will be informed by standardised data extraction tools such as the JBI data extraction tool – MASTARI - and the Cochrane data extraction tool, and another reviewer will check for any disagreements. A third review author will be consulted where necessary.

### Risk of bias (quality) assessment

The Newcastle-Ottawa Scale (NOS) for observational studies will be used to assess the risk of bias of the included studies by two review authors. Any discrepancies will be resolved by consultation within the review team

### Strategy for data synthesis

A minimum of two studies will be set to carry out quantitative data analysis and synthesis in this review. Data reported in the included studies in the form of mean, standard deviations, and statistical significance will be used as summary measures for children's cognitive outcomes less than eighteen years. The results' interpretation will be made using the pooled mean values and corresponding standard deviation and statistical significance of this pooled effect. Three researchers (BG, LA, MS) will be involved in quantitative data analysis using Comprehensive Meta-Analysis (CMA), version 3.0 (Biostat Inc., USA). Consultations with other reviewers will resolve any disagreement. Using Cochran's Q heterogeneity test and I<sup>2</sup> statistic, the extracted data's statistical heterogeneity will be explored.

### Analysis of subgroups or subsets

A subgroup meta-analysis will be performed based on the age, geographic location, and type of fluoride exposure in cases where there are enough homogeneous data available from the included studies.

### Contact details for further information

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### Organisational affiliation of the review

Teeside University

### Review team members and their organisational affiliations

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### Type and method of review

Meta-analysis, Systematic review

**Anticipated or actual start date**

27 January 2021

**Anticipated completion date**

02 August 2021

**Funding sources/sponsors**

None.

**Conflicts of interest**

**Language**

English

**Country**

England

**Stage of review**

Review Ongoing

**Subject index terms status**

Subject indexing assigned by CRD

**Subject index terms**

Child; Child, Preschool; Cognition; Fluorides; Fluorine Compounds; Humans; Minerals; Pregnancy

**Date of registration in PROSPERO**

02 February 2021

**Date of first submission**

27 January 2021

**Stage of review at time of this submission**

<b>Stage</b>	<b>Started</b>	<b>Completed</b>
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

**Revision note**

Since the initial search returned articles with limited or minimal relevant outcomes, it was decided to expand the age group of participants upto 18years and add an additional outcome (academic achievements)

*The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.*

*The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.*

### Versions

02 February 2021

21 May 2021